Last updated: 6/17/2026
Study Protocol

Title: Whole body metabolic activity as a reflection of tumor metabolic dysregulation and a predictor of treatment response in ovarian cancer.

Working Title: Metabolism as a predictor PROC

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Background

Epithelial ovarian, peritoneal, and fallopian tube carcinomas are the leading cause of gynecologic cancer-related morbidity and mortality in women [1]. Following a diagnosis of advanced ovarian cancer, patients are treated with a combination of cytoreductive surgery and platinum-taxane-based chemotherapy [2-4]. While the majority of patients will achieve remission without evidence of disease, more than 80% of patients will eventually recur[5]. Ultimately, almost all patients with recurrent disease will develop platinum-resistance. [6]. Women with platinum-resistant ovarian cancer have a poor prognosis with overall survival of <12 months [7, 8]. Treatment-free interval, the time from completion of one line of therapy to the initiation of a second line of therapy (platinum-based chemotherapy or otherwise), is recognized as a predictive and prognostic marker and is a frequent inclusion criterion for consideration of clinical trial enrollment[9]. There is an unmet need to further understand the mechanisms of platinum resistance and to identify biomarkers that predict resistance to platinum chemotherapy in ovarian cancer[10, 11]. A thorough understanding of tumor metabolism has the potential to predict those patients that will best respond to therapy and target patients with ovarian cancer who have the worst prognosis.

Historically, our understanding of the role of metabolic dysregulation in cancer cells began with the identification of the Warburg effect. In normal cells, efficient glucose metabolism proceeds through glycolysis followed by the tricarboxylic acid (TCA) cycle, and electron transport chain to utilize oxygen to generate energy in the form of adenosine triphosphate (ATP). Warburg reported that cancer cells showed a preference for glycolysis and lactic acid fermentation even in the presence of sufficient oxygen, termed aerobic glycolysis[12, 13]. In addition to a preference for aerobic glycolysis, several frequently expressed oncogenic mutations (*MYC, TP53, RAS*, and *PI3K* signaling pathways, among others) serve to alter glucose and glutamine metabolism across a variety of cancer types, allowing for increased bioavailability of energy but also building blocks for anabolic processes. Hypoxia and acidosis invariably develop within solid tumors due to inadequate perfusion. Signaling from these changes causes upregulation of the expression of fatty acid synthase and dysregulation of lipid metabolism in addition to inducing the dissociation of glycolysis from the TCA cycle[14, 15]. These changes can induce epigenetic and genetic alterations, leading to chemoresistance[14, 15].

In renal cell carcinoma, data from the Cancer Genome Atlas identified lactate-related gene expression as predictive of response to immunotherapy and cytotoxic chemotherapy as well as overall survival[16]. In breast cancer, trastuzumab works at least in part through inhibition of glycolysis via downregulation of heat shock factor 1 and lactate dehydrogenase[17]. However, extremely limited data is available regarding metabolic dysregulation in ovarian cancer. Studies have demonstrated an increased metabolic rate in patients with ovarian cancer compared to healthy volunteers [18-20]. Pyruvate dehydrogenase kinase (PDK) is an enzyme that allows the transition from glycolysis to oxidative phosphorylation, increasing the metabolic flexibility of cells; upregulation of this enzyme has been identified in drug-resistant ovarian cancer cell lines and PDK knockdown increased cisplatin sensitivity in these cells[21]. Serum from patients with ovarian cancer has also demonstrated markers of aberrant phospholipid metabolism; increased expression of fatty acid synthetase has been detected in the serum of ovarian cancer patients with platinum-resistant disease and may function through stabilization of the endoplasmic reticulum, protecting the cell from reactive oxygen species and improving cell survival[22, 23].

This proposal targets a previously unstudied method to predict ovarian cancer outcomes and advance our understanding of chemotherapy resistance. Measurement of whole-body metabolic activity offers a non-invasive method of determining response to therapy, potentially identifying patients who may benefit from multimodal therapy earlier.

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The pathway from which cells derive energy can be measured both directly and indirectly on a cellular or whole-body level. Direct calorimetry measures heat production and is considered the gold standard for the measurement of metabolic activity. However, direct calorimetry is costly and cumbersome. Indirect calorimetry approximates metabolic rate through the measurement of oxygen consumption and carbon dioxide production, allowing the calculation of oxygen consumption rate (an approximation of energy expenditure), respiratory quotient (an indirect measure of substrate utilization), and metabolic rate[24, 25]. Other indirect measurements include measuring glucose consumption and the serum metabolites of cellular energy pathways, including L-lactate, lactate dehydrogenase, citrate, and extracellular acidification. While *in vivo* animal models have been used to study tumor metabolic activity[26, 27]; these models necessarily either lack an intact immune microenvironment (patient-derived xenografts) or incompletely reflect tumor heterogeneity (syngeneic mouse models) [28, 29]. In addition, the correlation between whole-body metabolic activity and cellular metabolic processes within the ovarian cancer tumor microenvironment has not been established. Utilizing patient-derived *ex vivo* cellular models for flux analysis presents a unique opportunity in translational science to bridge findings from cell culture with patient-level data and clinical outcomes. The evaluation of cellular metabolites from our participants will allow us to understand how the data gathered here fits into previously published literature on cancer metabolism. RNA transcriptome data from cellular models will allow us to validate metabolomic measures and identify the predominant pathways utilized to facilitate the changes we measure at the whole-body level. In addition, in understanding the pathways involved in metabolic dysregulation of treatment-resistant ovarian cancer we may be able to target those metabolic pathways to restore response to therapy and initiate novel clinical trials targeting this patient population with urgent clinical need.

Study Objective:

We **hypothesize** that whole-body metabolic activity as measured via indirect calorimetry can be utilized as a non-invasive surrogate to reflect tumor metabolic dysregulation in patients with ovarian cancer. Moreover, we **hypothesize** that there will be an inverse relationship between treatment-free interval and the metabolic rate when measured at a whole-body level and an increased rate of glycolysis when measured within the tumor microenvironment. To address these hypotheses, we will pursue **specific aims** as listed below:

Primary objectives:

Aim 1: To delineate commonly utilized tumor metabolic alterations in ovarian cancer. These metabolic alterations will be explored for potentially targetable pathways to restore chemotherapy responsiveness.

Aim 2: To define the relationship between whole-body metabolic activity as measured via indirect calorimetry with ex vivo measure of tumor metabolic activity.

Secondary objectives:

Aim 3: To evaluate longitudinal changes in whole-body metabolic activity over the course of cytotoxic chemotherapy and evaluate these changes as they relate to oncologic outcomes and treatment-free interval.

Aim 4: To examine the impact of tumor metabolic alterations on healthy non-malignant tissues and serum metabolites. We will use an integrated approach coupling non-invasive measures of whole-body metabolic activity via indirect calorimetry with ex vivo measures of tumor metabolic activity via functional studies on patient-derived cell models and unbiased metabolite measures. The knowledge gained will lay the critical framework to evaluate these diverse measures of metabolism as they relate to each other and will ultimately lead to improved prognostication for our patients. We are optimistic that the data gained will support future extramural funding and novel clinical trials.

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Aim 5: An additional exploratory objective is to collect data that will contribute to a more holistic understanding of the whole-body metabolic effects of ovarian cancer. Based on prior studies, surveys have been an effective method for capturing the social, psychological, and behavioral factors associated with the disease. It is possible that changes in metabolism and inflammation are mediated by these psychosocial factors that ultimately impact response to cancer therapy.

Outcomes Assessed:

Primary study outcome measures

- Change in metabolic measurements over the course of cancer treatment
    - Five metabolic measurements will be completed (prior to treatment [SV1], after debulking surgery [SV3], prior to cycle #3 chemotherapy [SV4], prior to cycle #6 chemotherapy [SV5], and 6 months after completion of chemotherapy [SV7])
    - Change in resting metabolic rate
    - Change in respiratory quotient
    - Change in carbon dioxide production
    - Change in oxygen consumption
- Change in metabolic flexibility (change in the outcomes listed above from the fasting to a postprandial state) over the course of treatment
    - Two metabolic flexibility measurements will be completed (prior to treatment and 6 months after completion of chemotherapy)
    - Patients will consume a high-fat shake and post-prandial metabolic measurements will be collected
- Ability to isolate tumor stem cells and perform ex vivo expansion
- Ability to collect fresh tumor explants for evaluation
- Cellular oxidation and mitochondrial function of established primary cell lines and fresh tumor tissue

Secondary study outcome measures

- Baseline markers of metabolism in blood (i.e., blood lipids, insulin, glucose, lactate, and free-fatty acids)
- Relationship between whole-body metabolic rate and tumor cellular oxidation and mitochondrial function as measured via XFe24 Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, MA).
- Cellular oxidation and mitochondrial function of benign skeletal muscle and fat tissue from selected patients measured via XFe24 Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, MA).
- Oncologic outcomes:
    - Progression-free survival (PFS, the time to disease recurrence or death after completing chemotherapy)
    - Treatment-free interval (TFI)
    - Circulating tumor DNA which will be evaluated in post-hoc fashion so as not to impact standard of care treatments
- Relationship between whole-body metabolic activity and oncologic outcomes
- Relationship between whole-body metabolic activity and circulating tumor DNA
- Patient-reported quality-of-life measures

Tertiary study outcome measures

- Relationship between whole-body metabolic activity and social, psychological, and behavioral factors. The following outcomes will be assessed via surveys:
    - Disease-related symptoms
    - Quality of life
    - Physical Activity
    - Fatigue
    - Social Support

Other data points to be collected

- Weight (objectively assessed)
- Height (objectively assessed)
- Body Composition (objectively assessed)
- Anthropometric Assessment (objectively assessed)
- Blood Pressure (objectively assessed)
- Heart Rate (objectively assessed)
- Date of birth (EMR extraction)
- Age (self-reported)
- Race (self-reported)
- Ethnicity (self-reported)
- MRN (EMR extraction)
- Treatment Plan (EMR extraction)
- Medications and/or other conditions that may influence metabolism (EMR extraction)
- Dietary intake summary (self-report)
- Fasting yes/no (if not fasting, we collect information about the meals they consumed)
- Meals consumed the night before study visit (self-reported)

Description of Surveys

Surveys will be delivered to participants electronically during several study visits [SV1, SV4, SV7] via REDCap. Study data will be collected and managed using REDCap electronic data capture tool (PMID 31078660) hosted by the University of Tennessee Health Science Center College of Medicine Knoxville.

Participants will be given a tablet during study visits to collect survey responses and will have the option to start and stop the electronic surveys. Survey administration will be staggered to prevent undue time toxicity for the participants. It is estimated that no more than 30 minutes will be required to complete questionnaires at any one time.

The planned questionnaire consists of an amalgamation of multiple previously published and/or validated surveys and include the following:

- Surveys administered during the first and final study visit:
    - The National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index (NCCN_FACT FOSI-18), which assess disease-related symptoms (18 questions, 5-10 minutes)[30].
    - NCI Percentage Energy from Fat Screener (used to get a summary of dietary intake) (17 questions, 5-10 minutes)[31].
    - Multifactor Screener in Observing Protein and Energy Nutrition (OPEN) Study (16 questions, 5-10 minutes), which assesses fiber intake and fruit and vegetable intake[32].

- International Physical Activity Questionnaire (IPAQ) (7 questions, 3-5 minutes), which assesses the type of physical activity and sitting time[33].

- Surveys administered at chemotherapy cycle #3 (mid-point of therapy):
  - WHOQOL-BREF questionnaire, which is a self=assessment of quality of life within the context of an individual's culture and value systems (26 questions, 10-15 minutes)[34].
  - PROMIS-29 questionnaire which assesses physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities (29 questions, 5-10 minutes) [35].
  - Social Provisions scale, which assesses perceived support of social relationships (10 questions, 5 minutes)[36].

Study Design

This is an exploratory, prospective study designed to collect metabolic measures and correlate those to analyses of the tumor microenvironment and treatment response. This study will be a pilot study, allowing us to optimize the collection and processing of tumor tissue. Exploration into the relationship of whole body metabolic measures and tumor metabolic measures will inform our analyses of these parameters going forward, and has not previously been studied in this patient population.

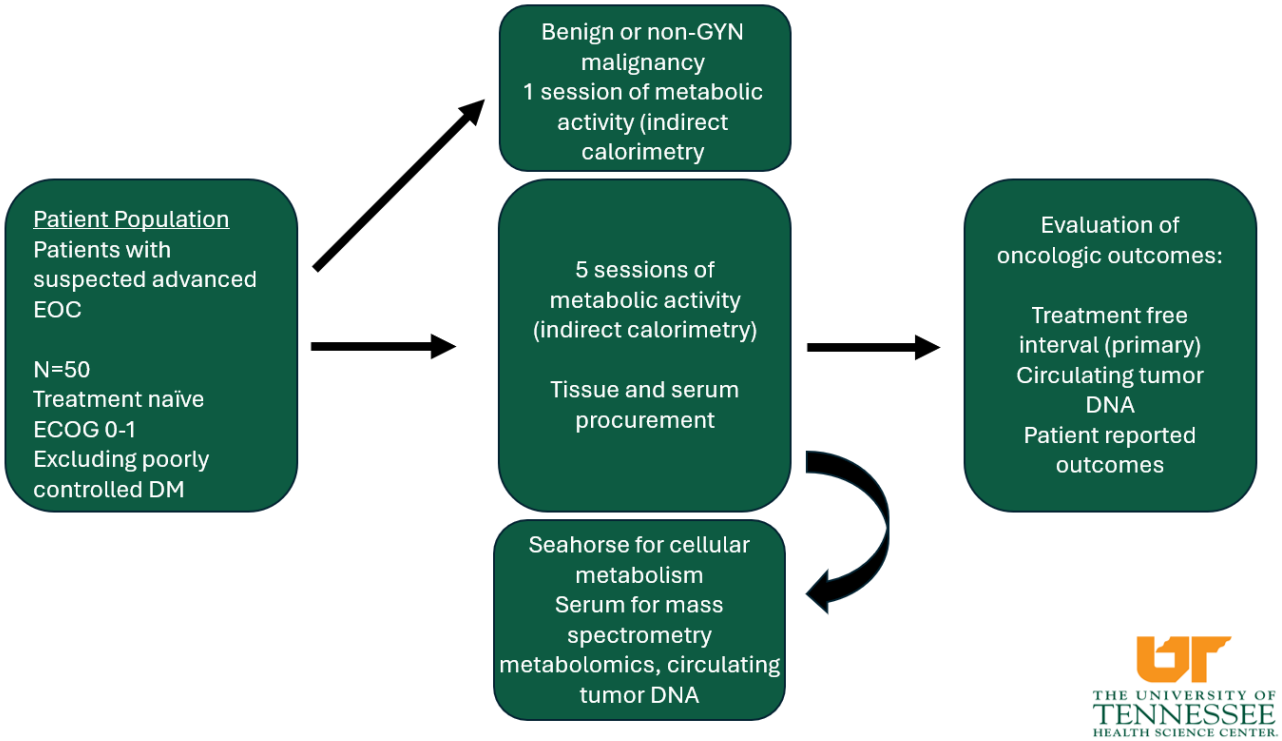


Figure 1. Study Overview

Study Schema

1. Potential participants will be identified by their physician and/or clinical staff, every effort will be made to enroll a diverse group of participants representative of our patient population. During a patient encounter with a potentially eligible patient, the provider may briefly describe the study and get verbal

consent for a research team member to follow up with them using their preferred contact information. The provider may also offer to go through the informed consent process during their visit.

a. Alternatively, patients identified by their providers (if face-to-face recruitment is not feasible) will be sent a standardized letter informing them that they may be eligible for a study and will be contacted by a provider.
b. If needed, the study will be advertised using flyers in clinics using flyers that would be submitted to and approved by the IRB.
    i. Patients who see study advertisements may contact the study team directly.

2. The research team will screen the patients identified by their providers, using the patient's medical record and a checklist developed by the research team that maps onto the inclusion/exclusion criteria, to ensure they meet all inclusion criteria and none of the exclusion criteria.

3. It is anticipated that in most cases, a research team member will contact potential participants via their preferred method of communication or face-to-face. The research team member will describe the study in more detail so that the potential participant fully understands the study and the participation commitments.

4. A meeting time/day will be set for the consent process or completed during the same interaction.

5. Participants will meet with a study team member either in person, virtually, or via phone call to complete the consent process. Consent will be obtained using an electronic signature via REDCap or face-to-face with pen and paper on a paper consent form.

6. The date of all study visits (7 in total) will be discussed with the patient in conjunction with the patients anticipated chemotherapy schedule.
    a. If a patient who is enrolled in the study is found to have non-gynecologic malignancy or benign pathology at the time of surgery no further study visits will be completed post-operatively.

7. There are a total of 7 Study Visits planned (*See Study Visit Overviews and Table 1 for specific details*).
    a. Five study visits will include whole body metabolic assessments:
        i. Prior to initiation of therapy or before surgical debulking (SV1)
        ii. Four to six weeks after surgical debulking before initiation of adjuvant chemotherapy (this timing is part of standard of care) (SV3).
        iii. Prior to cycle #3 chemotherapy (SV4). This study visit would occur in conjunction with chemotherapy visit.
        iv. Prior to cycle #6 chemotherapy (SV5). This study visit would occur in conjunction with chemotherapy visit.
        v. Six months after completion of chemotherapy (SV7).
    b. An additional two study visits (SV2 and SV6) will consist of vital sign and anthropometric assessments and blood draws.
        i. These study visits will occur for the procurement of blood for future ancillary testing (circulating tumor DNA, serum metabolites). The research team has decided that banked blood will only be analyzed after the conclusion of research participation to minimize research implications for clinical care given the analysis of circulating tumor DNA is experimental in ovarian cancer.
        ii. Prior to surgical debulking (SV2) this study visit will only be necessary if neoadjuvant chemotherapy was performed prior to surgery. If no neoadjuvant chemotherapy was

recommended by the participants clinician this study visit will not be necessary and will occur with SV1.

iii. Three months after completion of chemotherapy (SV6).

c. Every effort will be made to minimize travel/time burden on participants and coordinate study visits alongside clinical care while not impacting clinical care delivery.

8. Direct patient participation in the study ends. The EMR will be monitored every 6 months until disease recurrence to collect oncologic outcomes data on all participants (progression free survival, treatment free interval).

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Study Visit Overviews

Study Visit 1 and 7 – Metabolic Flexibility Assessment with Meal Challenge (see Table 1)

The study visit activities will occur in the Physical Activity and Metabolism (PAM) Lab in Suite 206 in Medical Building B on the UTMC campus.

1. On study visit day, research team will meet with the participant at the Physical Activity and Metabolism (PAM) Laboratory.
2. Participants will present fasted (water and decaffeinated coffee permitted) from midnight the night prior.
3. Blood will be drawn for research purposes via a single stick. The participant's weight and height and baseline vitals will be collected.
    a. A total blood volume of approximately 32 mL will be collected to assess biomarkers of metabolism and for post-hoc measurement of circulating tumor DNA.
4. Following a resting period and before consuming the optional high-fat smoothie, metabolic measurements will be assessed for 15-20 minutes using the TrueOne Canopy Option and TrueOne Metabolic Cart (TrueOne 2400, Parvomedicas, Sandy, UT). See Figure 2.



Figure 2. Image of participant from previous study conducted in the PAM Lab undergoing metabolic assessment.

5. Following the collection of resting metabolic measurements, participants will consume a standardized 490 kcal high-fat smoothie, consisting of 57% fat, 23% carbohydrate, and 20% protein.
    a. The ~12 ounce smoothie consists of a Boost high protein shake, 5 tablespoons of heavy whipping cream and 3 ice cubes.
    b. Similar high-fat meal challenges have been used to assess lipid metabolism and metabolic flexibility in other published studies and in our Lab's previous metabolic flexibility study in patients with ovarian cancer.
    c. Participants will be asked to complete the high-fat smoothie in approximately 5 minutes.
    d. The study team will measure any volume that is not consumed and will record the amount of time taken to consume the smoothie.

e. e. Participants may decline participation in the meal challenge and remain eligible to participate in all other study procedures.

6. Postprandial metabolic measurements and resting vitals will be collected at 1 hour and 2 hours post meal.
    a. During the entire 3-hour study period, participants will be asked to remain reclined or seated and resting.
    b. Also, body composition (assessed via BIA) and skinfold thickness at 7 sites and other anthropometric measurements (upper arm, waist, hip, and thigh circumference) will be completed between the postprandial metabolic assessments.
    c. Participants are allowed to use the restroom and drink water during the study visit as needed.
7. Resting vital signs (e.g. blood pressure, heart rate) will be at baseline and also assessed 1 hour and 2 hours post meal.
8. Participants will complete the study surveys during study visit downtime.
9. An overview of the 3-hour study visit is presented in Figure 3.

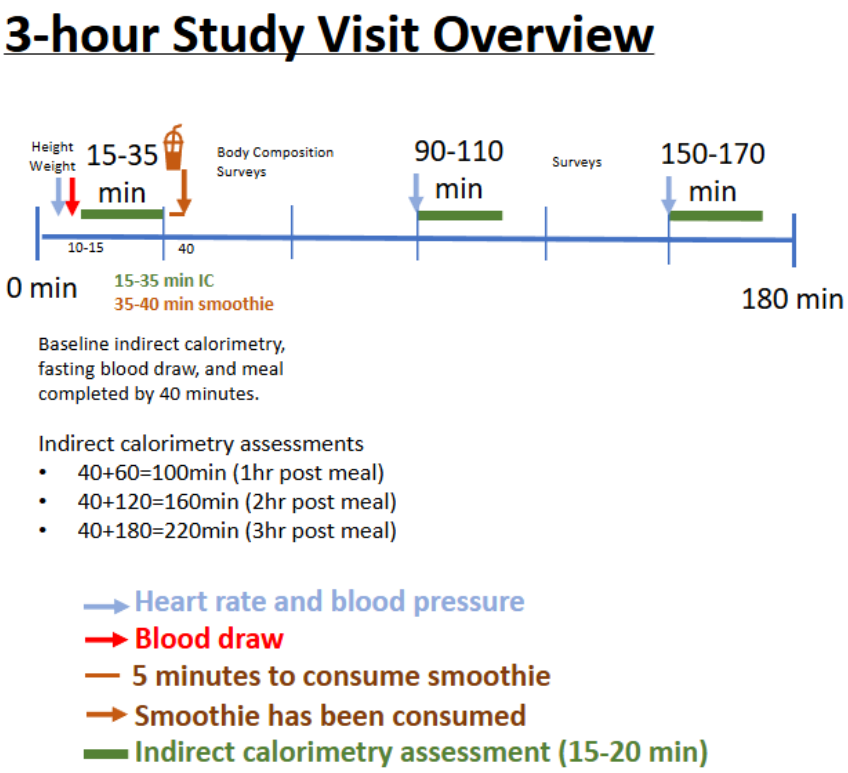


Figure 3. Study Visit 1 and 7 Overview.

Study Visit 2 and 6 (see Table 1)

The study visit activities will occur in the UTMC Cancer Institute building or main hospital.

1. Participants will present fasted (water and decaffeinated coffee permitted) from midnight the night prior.

2. Standard of care labs will be drawn. Additional blood will be drawn at that time for research purposes via a single stick.
    a. A total blood volume of approximately 32 mL will be collected to assess biomarkers of metabolism and for post-hoc measurement of circulating tumor DNA.
3. The participant's weight and height will be collected as part of standard of care.
4. Resting vital signs (e.g. blood pressure, heart rate) will be assessed.

Study Visit 3 (see Table 1)

The study visit activities will occur in the UTMC Cancer Institute building.

1. On study visit day, research team will meet with the participant at the oncology clinic.
2. Participants will present fasted (water and decaffeinated coffee permitted) from midnight the night prior.
3. Standard of care labs will be drawn by LabCorp personnel. Additional blood will be drawn at that time for research purposes via a single stick either via accessing a patient's chemotherapy port for clinical purposes or via venipuncture.
    i. A total blood volume of approximately 32 mL will be collected to assess biomarkers of metabolism and for post-hoc measurement of circulating tumor DNA.
    ii. If blood cannot be coordinated with clinical purposed and patient declines venipuncture this will be an expected protocol deviation and no additional sticks will be performed.
4. The participant's weight and height will be collected as part of standard of care.
5. Following a resting period and before chemotherapy infusion, metabolic measurements will be assessed for 15-20 minutes using the TrueOne Canopy Option and TrueOne Metabolic Cart (TrueOne 2400, Parvomedicas, Sandy, UT).
6. Resting vital signs (e.g. blood pressure, heart rate) will be assessed following the metabolic measurement.

Study Visit 4 & 5 (see Table 1)

The study visit activities will occur in the UTMC Cancer Institute building.

1. On study visit day, research team will meet with the participant at the oncology clinic.
2. Standard of care labs will be drawn by LabCorp personnel. Additional blood will be drawn at that time for research purposes via single stick.
    a. A total blood volume of approximately 32 mL will be collected to assess biomarkers of metabolism and for post-hoc measurement of circulating tumor DNA.
3. A research team member will collect the participant's weight and height.
4. Following a resting period, baseline metabolic measurements will be assessed for 15-20 minutes using the TrueOne Canopy Option and TrueOne Metabolic Cart (TrueOne 2400, Parvomedicas, Sandy, UT).
5. Resting vital signs (e.g. blood pressure, heart rate) will be assessed following the metabolic measurement.
6. Thirty minutes after the start of the infusion of a drug of interest (cytotoxic chemotherapy or immunotherapy agent) begins, a second metabolic measurement will be assessed for

15-20 minutes using the TrueOne Canopy Option and TrueOne Metabolic Cart (TrueOne 2400, Parvomedicas, Sandy, UT).

7. Resting vital signs (e.g. blood pressure, heart rate) will be assessed following the metabolic measurement.
8. Metabolic measures and vital sign measures will be collected (as described in steps 7-8) at one additional time point during the study visit (at 90-minutes post infusion of drug of interest).
9. During the study visit downtime:
    a. Participants will complete the study surveys during study visit down time during SV 4.
    b. Body composition and skinfold thickness at 7 sites will be measured and other anthropometric measurements (upper arm, waist, hip, and thigh circumference) will be completed during SV5.
10. Participants will be allowed to use the restroom and drink water during the study visit as needed.
11. An overview of the study visit is presented in Figure 4.

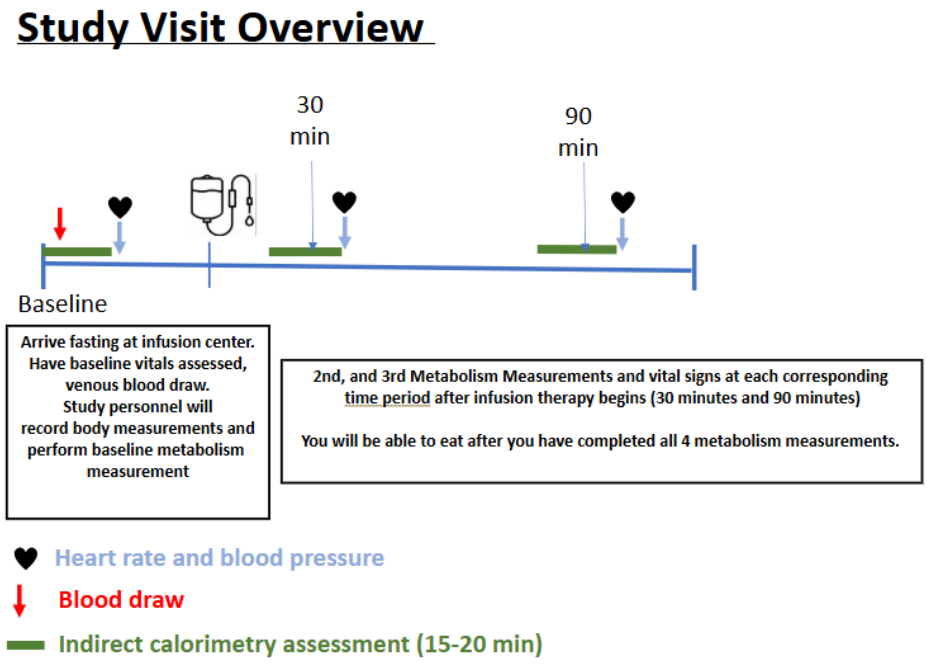


Figure 4. Study Visit 4 and 5 Overview.

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Additional Protocols

Tumor Collection

1. Tumor tissue will be collected in conjunction with the University of Tennessee Medical Center Pathology Department.
2. At the time of tumor debulking surgery, performed via standard of care indications, after specimen removal, viable tumor tissue will be grossly confirmed by pathologist.
3. Approximately 2.5cm^3 segment of tumor tissue will be selected for study purposes from either the ovary (preferred) or omentum as long as removal of tumor tissue will not interfere with accurate pathologic assessment for clinical purposes.
4. Tumor tissue selected for study purposes will be divided equally and a portion of the tissue will be maintained fresh in medium; the remainder will be flash frozen.
    a. The University of Tennessee Medical Center Pathology Department will be utilized for collection of tumor tissue and maintenance of frozen tissue specimens.
    b. Fresh Tumor tissue will be transported by study personnel to the lab of Dallas Donohoe, PhD (Associate Professor within the Department of Nutrition at the University of Tennessee Knoxville).
5. Additionally, a 50-100 mg biopsy of rectus abdominus muscle and 50-100mg biopsy of subcutaneous adipose tissue will be collected from patients for comparator studies evaluating benign tissue.
    a. This will involve no additional surgical incision and is not a clinically meaningful volume which would impact wound healing.
    b. Tissue will be transported by study personnel to the lab of Tom Massi, PhD (Associate Professor within the Division of Surgical Research, Department of Surgery University of Tennessee Health Science Center, Knoxville).
    c. The cells will be cultured in conjuncture with Dr. Tom Massi and stored for future ancillary studies.
6. Specimens will be de-identified and assigned a research identification number.

Ex vivo metabolic studies

1. Fresh and flash frozen tumor tissue and benign skeletal muscle and adipose will be utilized for cellular metabolic studies using the XFe24 Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, MA) at the Donohoe lab within the Department of Nutrition at the University of Tennessee Knoxville.
    a. XFe24 Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, MA) will be used to measure oxidation and mitochondrial function.
    b. The oxygen consumption rate will be calculated. The proportion of ATP-coupled mitochondrial respiration will be derived using a mitochondrial stress assay in which oligomycin is used to block ATP synthase. The spare respiratory capacity will be estimated using FCCP ionophore which uncouples respiration from ATP synthesis and allows estimation of oxidative phosphorylation. Non-mitochondrial metabolism will be estimated using antimycin and rotenone to block mitochondrial respiration[37].
2. Ancillary studies will be pursued to analyze metabolic dysregulation using surplus tissue and samples collected to evaluate metabolomic measures.
3. All biologic material will be completely de-identified for off site collaborators and assigned a separate study identifier.

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Participant Selection, Enrollment, and Withdrawal

Study population: The study population includes patients with suspected epithelial ovarian cancer. Specific inclusion and exclusion criteria are listed below.

Inclusion Criteria

- Women
- Age >18 years
- Suspected of having epithelial ovarian cancer by the provider
- No prior cytotoxic therapy for ovarian cancer
- Surgical debulking is planned
- ECOG performance status 0-1

Exclusion Criteria

- Inability to provide voluntary informed consent.
- Received medical intervention for adverse effects of chemotherapy.
- Circumstances and/or medical conditions that would limit compliance with study requirements and protocol, as determined by the principal investigators.
- Poorly controlled diabetes, hemoglobin A1C ≥9%

Participant Recruitment and Screening

Participants will be recruited primarily by physician and/or medical provider referral from UT Gynecology/Oncology. Medical care providers treating women with gynecologic cancer will ask patients if they are interested in participating in the study and are willing to be contacted by the research team. Medical care providers may verbally gather this information from patients during clinic visits. Patients may also be contacted by their medical providers electronically or by phone. Patients could be contacted by a medical provider and or research team members about the study by phone or electronically (not in person). Patients may also be sent a standardized letter outlining they may be eligible for participation.

Participants could also be recruited by contacting potentially eligible participants. Using electronic medical records, research team members will contact participants who meet the medical inclusion/exclusion criteria, after they have provided verbal or written consent (to a clinical staff person or provider) that they are willing to be contacted by a research team member.

If the patient consents to being contacted by the research team, the medical provider and/or clinical staff person will forward the patients name and preferred contact information and any other relevant information about the patient's preferences/background to the study team. Using the patient's contact information, the study team will contact the patient to describe the study in more detail. If the participant does not reply, a study team member will follow-up the second week with a phone call. The third week, if there is no reply, a study team member will follow up with a third and final phone call.

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If the participant declines to participate at any time point, all follow-up contact attempts will stop.

It may also be that the patient wishes to learn more about the study on the same day as a clinic visit. If feasible, a research study team member will make every effort to meet the potential participant in the clinic to explain the study (either in a low traffic/private area in the clinic or in a low traffic/private area on the medical center campus).

During this contact with the potential participant, the research team member will screen for participation/eligibility, using the potential participant's self-reported answers to screening questions to determine inclusion/exclusion criteria, which will be confirmed with later follow up using the participant's medical record. The study team members will also gather information about the patient's availability/schedule for scheduling the first study visit.

If the potential participant expresses continued interest in the study, the study team member will take them though the consent document.

If a second wave of recruitment is necessary to obtain recruitment goals, flyers advertising the study will also be posted in clinics that treat women with ovarian cancer (after the flyers are submitted to and approved by the IRB). Potential flyers will list an email contact for the study team member. Potential participants will email the study team member and a time to talk about the study in more detail will be arranged via email communications.

Enrollment
We aim to enroll up to 50 participants in this study. A power analysis was performed. Using a two-tailed hypothesis, a hypothesized correlation (r = 0.5) between metabolic rate and platinum-free interval, an alpha value of 0.05, 80% power, and a null hypothesis of r = 0.0, a total of n = 29 patients with epithelial ovarian cancer will be needed to have adequate power for the study.

It is estimated that ≤20% of patients suspected of having epithelial ovarian cancer will have benign pathology or non-GYN malignancy. These patients will be included as a control but will only undergo the pre-treatment metabolic measure and tissue collection and will not undergo any other study interventions.

Additionally, an approximately 20% attrition rate is expected.

We anticipate that enrollment will take approximately 2 years.

Our goal will be to enroll a diverse patient population reflective of our local demographics.

Participant Compensation

Participants could receive up to $325 for completing all study requirements.

- The following is a breakdown of compensation:
    - $75 for completing all of SV1 ($50 if the study participant chooses to not complete the meal challenge)
    - $100 for completing all of SV3
    - $50 for completing all of SV4
    - $50 for completing all of SV5

- $125 for completing all of SV7 (75$ if the study participant chooses to not complete the meal challenge)

Duration of Study Participation

The duration of direct study participation will include the duration of chemotherapy administration and 6 months of follow-up after chemotherapy. This is estimated at approximately 12-15 months for the majority of participants. In addition, clinical outcomes will be followed for up to 2 years after completion of chemotherapy to monitor for disease recurrence.

The standard of care for ovarian cancer patients is to begin chemotherapy 3-8 weeks post-surgery. The standard treatment plan post-surgery is for patients to receive 6-8 cycles of a combination of taxane/platinum chemotherapy every 3 weeks.

Withdrawal and Lost to Follow-Up

Participants may be withdrawn from the study prior to the expected completion for the following reasons:

- Failure of the participant to adhere to protocol requirements.
- Participant consent withdrawal
- The participant's medical provider feels it may be in the participant's best interest to stop participation.
- Chemotherapy related infusion reaction precluding collection of data.

Informed Consent

After the patient has been screened and eligibility and availability has been confirmed, the participant will sign a consent form virtually (in REDCap) or using pen and paper (face-to-face).

The participant will be emailed a copy of the completed/signed informed consent for their records and the study team will store a copy of the complete/signed informed consent in a secure OneDrive folder.

If the consent process occurs via phone or virtually, a copy of the consent form will be emailed or texted or mailed to the potential participant prior to the phone or virtual consent meeting, so that the participant is able to view the consent document during the consent process.

Alternatively, if a potential participant expresses an interest in the study during a clinic visit on the medical center campus, and a study team member is available, a study team member will meet with the potential participant the same day. If feasible, a research study team member will make every effort to meet the potential participant in the clinic to explain the study (either in a low traffic/private area in the clinic or in a low traffic/private area on the medical center campus). The potential participant will have the opportunity to complete the informed consent electronically using REDCap in person or using a paper copy of the consent. In either case, a signed consent document will be given to the participant for their records. Signed consent copies will be given to the participant in the form of text, email or hard copy (paper), depending on their preference.

As part of the informed consent process, the individual is told that participation in the study is voluntary, and that consent to participate may be withdrawn at any time. If the participant wishes to withdraw their consent, the PI must be notified.

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Safety and Adverse Events

Definitions

Adverse Event

An *adverse event* (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be assessed for likelihood of association to study interventions by PI. Abnormal responses to an intervention session could be considered an adverse event if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to clinical treatment
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A *serious adverse event* is any AE that is:

- fatal
- life-threatening
- requires a clinical or hospital visit
- results in persistent or significant disability or incapacity
- an important medical event

Non-Serious Adverse Event

All adverse events that do not meet any of the criteria for serious should be regarded as *non-serious adverse events*.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Screening Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will be recorded and documented as an adverse event.

Adverse Event Reporting Period & Reporting

The research study is an observational study with no intervention. Therefore, there are no expected adverse events or serious adverse events for this study. AEs or SAEs deemed by the PI to be unrelated to study will be monitored at each study visit and all SAE will be reported to the IRB. The PI will contact the IRB and provide them with a copy of the SAE Form (See Appendix A).

Statistical Considerations

While the prospective nature of participant enrollment offers the unique opportunity to obtain tissue as part of standard-of-care treatment for ovarian cancer without additional invasive interventions, prospective enrollment does present inherent challenges. While only patients with suspected advanced-stage ovarian cancer will be enrolled, not all cases with suspected ovarian cancer will have invasive malignancy on final pathology. We feel that the inclusion of patients with benign pathology will offer a valuable opportunity to standardize findings. The heterogeneous nature of ovarian cancer must be considered and patients with histology other than high-grade serous may have different alterations in metabolic activity which could potentially confound the data. In addition, prospective enrollment at the time of initial diagnosis offers inherent blinding during the collection of study data as most patients develop platinum-resistance at the time of recurrent disease.

Additional considerations include barriers to patient enrollment. Using a two-tailed hypothesis, a hypothesized correlation ($r = 0.5$) between metabolic rate and platinum-free interval, an alpha value of 0.05, 80% power, and a null hypothesis of $r = 0.0$, a total of $n = 29$ patients with invasive malignancy will be needed to have adequate power for the study. We plan to enroll 30 patients with confirmed invasive malignancy. It is estimated that ≤20% of patients suspected of having epithelial ovarian cancer will have benign pathology or non-GYN malignancy. These patients will be included as a control but will only undergo the pre-treatment metabolic measure and tissue collection, and will not undergo any other study interventions. Additionally, an approximately 20% attrition rate is expected.

Statistical Methods

Data will be analyzed using descriptive statistics and normality will be assessed for continuous variables using Kolmogorov-Smirnov tests. Pearson product-moment correlation coefficients for normally distributed variable or Spearman's rank-order correlation coefficients for non-normally distributed variables will be used to assess the degree of the relationship between variables. Partial correlations will be used to adjust for potential confounders. Paired t-test will be used to assess change in metabolism measurement.

Ethical Considerations

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures.

This protocol and any amendments will be submitted to the IRB. The decision of the IRB concerning the conduct of the study will be made in writing to the PI and a copy of this decision will be provided to the sponsor before commencement of this study.

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study.

The consent form will be submitted with the protocol for review and approval by the IRB for the study.

The formal consent of a participant, using the IRB-approved consent form, will be obtained before that participant is submitted to any study procedure. This consent form will be electronically signed by the

participant and the research team member obtaining the consent using REDCap or signed using a wet signature if consenting is conducted in person.

Data Handling and Record Keeping

Confidentiality
Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).
Participants will sign an authorization that informs the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

Data and Records
For participant recruitment and enrollment, an excel file will be maintained by the PI. It will be stored in OneDrive and password protected and only accessible to approved research team members on UT Health science center campus.

All enrolled participant data will be maintained in the secured and HIPAA compliant REDCap system. Participants will be assigned a study identification number. All biologic specimens will be labeled with study identification number and will be completely de-identified. Only approved research team members on UTMC campus will have access to PHI. No PHI will be shared with research team members outside of UTMC campus.

Funding Source
The research team has been funded by UT Health Science Center Cancer Institute grant.

Publication Plan

Results from this pilot study will be published in a peer-reviewed journal that is indexed in PubMed.

Last updated: 6/17/2026

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Table 1

Study Period	Screening	Study Participation					Follow-up	
Cycle Number		SV 1 - Pre-Treatment	SV 2 - Prior to debulking surgery	SV 3 - 4-6 wks after debulking surgery	SV 4 - Cycle #3 chemotherapy	SV 5 - Cycle #6 chemotherapy	SV 6 - ~3 months after chemotherapy	SV 7- ~6 months after chemotherapy
Verify eligibility	X							
Informed consent	X							
Demographic and medical history	X							
ECOG status	X							
Physical examination (height and weight)		X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X
Assessment AE and SAE		X	X	X	X	X	X	X
Body composition measurements		X				X		X
Blood draw - circulating tumor DNA		X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)
Blood draw - serum metabolic measures		X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)	X (16 mL)
Resting Metabolic Rate		X		X	X	X		X
High-fat shake and post-prandial metabolic measures (*optional)		X*						X*
Post-Chemotherapy metabolic measures					X	X		
Patient-reported survey data		X			X			X

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Appendix A

Serious Adverse Event (SAE)
Report Form

STUDY NAME

Last updated 1/31/2023

Protocol Number:_____

Site Name:_____

Pt ID:_____

Date Participant Reported/Date of Site Awareness:

___ ___ / ___ ___ ___ / ___ ___ ___ ___

d d m m m y y y y

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1. SAE Event Term (Diagnosis, ex: Stroke, Myocardial Infarction).
2. SAE onset date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
3. SAE stop date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
4. Location of SAE:_____
5. Was this an unexpected adverse event? ☐ Yes ☐ No
6. Brief description of the nature of the SAE (attach description if more space is needed):

   _____

   _____
7. Category of the SAE:
   - ☐ Date of death ___/_____/_____ (dd/mmm/yyyy)
   - ☐ Life threatening
   - ☐ Hospitalization – initial or prolonged
   - ☐ Disability/incapacity
   - ☐ Congenital anomaly/birth defect
   - ☐ Required intervention to prevent permanent impairment
   - ☐ Other:

8. Relationship of event to intervention:
   - ☐ Unrelated (clearly not related to the intervention)
   - ☐ Possible (may be related to the intervention)
   - ☐ Definite (clearly related to the intervention)

9. Was study intervention discontinued due to event? ☐ Yes ☐ No

10. What medications or other steps were taken to treat the SAE?

    _____

11. List any relevant tests, laboratory data, and history, including preexisting medical conditions.

    _____

12. Was this event a study related endpoint?
13. Type of report:
    - ☐ Initial
    - ☐ Followup
    - ☐ Final

Signature of principal investigator: Date:

_____ _____